Editorial

How should clinicians manage metastatic non-small cell lung cancer patients with *BRAF* non-V600E mutations?

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In the current era of broad molecular testing clinical management of non-small cell lung cancer (NSCLC) patients with *BRAF* non-V600E mutations may be a challenge as no effective targeted therapies are available. Abuali and colleagues have successfully tried to create a handy oversight of treatment approaches together with highlighting several distinctions between NSCLC with *BRAF* V6000E and *BRAF* non-V600E (1).

All *BRAF* mutations in NSCLC are estimated to 2–4% and the incidence of *BRAF* non-V600E mutations is higher than *BRAF* V600E (2,3). Some distinctions between *BRAF* V600E and *BRAF* non-V600E have been determined leading to develop three classes of *BRAF* mutations defined by kinase activity, potency to dimerization and depending on RAS-signaling. Basically, class I, II and III are corresponding to different *BRAF* non-V600E mutations, precluding only *BRAF* V600E mutation in class I. However, *BRAF* non-V600E seems to be a heterogenous disease with a lot of undetermined mutational variants, including also variants of unknown significance (VUS) (4). *BRAF* non-V600E mutations are rare coexisting with other mutations like *PIK3A*, *KRAS* or *TP53* (5). *BRAF* V600E mutations, however, may emerge as an acquired tyrosine kinase receptor (TKI)-resistance mechanism in patients with oncogene-addicted NSCLC, while acquired *BRAF* non-V600E are reported sporadically (6-8).

As the value for clinical prognostication of *BRAF* mutations is not established, we can practically use the distinction between *BRAF* V600E and *BRAF* non-V600E taking possibility of targeted treatment for *BRAF* V600E as a proxy for better outcome. However, median time-to-treatment-failure with *BRAF*-targeting agents seems to be shorter as compared to approved targeted therapy of other oncogenic drivers. NSCLC patients with *BRAF* non-V600E are prone to get poorer outcome than the patients with *BRAF* V600E, but some *BRAF* non-V600E variants may also respond to Vemurafenib or Dabrafenib/Trametinib or Sorafenib. Abuali *et al.* also discuss the role of check point inhibitors (CPIs) and show that patients with *BRAF* non-V600E are prone to respond slightly better to CPIs than the patients with *BRAF* V600E. Furthermore, class I appear to be less susceptible to immunotherapy than *BRAF* class II/III mutations. Regarding effect of chemotherapy for the whole *BRAF* NSCLC population, the better outcome is observed in *BRAF*-wild type NSCLC, and *BRAF* non-V600E NSCLC patients seem to respond slightly better than for *BRAF* V600E NSCLC patients.

Reassuming, the keynote of this article is to enable *BRAF* non-V600E NSCLC patients for early enrollment into currently ongoing trials, followed by standard immunotherapy with or without chemotherapy according to guidelines for non-oncogene-addicted NSCLC. Every *BRAF* non-V600E variant should be carefully assessed to find a feasible option for targeted therapy in second line or

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further. Despite of the fact that many aspects of *BRAF* non-V600E NSCLC remain unclear, we can use this compact review to get an idea how to manage this group of patients before clinical trials reveal effective treatment options.

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